

## ASCORBIC ACID (VITAMIN C) TREATMENT OF WHOOPING COUGH\*

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WHOOPING cough is an almost universal infectious disease, with its greatest infectivity in pre-school and school children. While some protection has been afforded against it by vaccination, treatment of the active disease has not progressed as has treatment of other infectious diseases such as scarlet fever and diphtheria. Madsen<sup>1</sup> reports that, of 1,842 vaccinated children, about 25 per cent escaped infection, while of 446 non-vaccinated children less than 2 per cent escaped. This decided improvement warrants the use of vaccines, but still leaves the infected child confronted with some weeks of unpleasantness and a not inconsiderable mortality rate. According to Tice,<sup>2</sup> in the registration area of the United States there were 7,518 deaths in 1934. In the years 1932-34 there were 45,755 cases of whooping cough reported to the Dominion Bureau of Vital Statistics, with 1,982 deaths. Of the fatal cases over 50 per cent occur in the first year of life. The non-fatal cases undergo a most disagreeable experience and lose considerable time from studies, in the case of the school-child. The disease is characterized by spasmodic coughing and vomiting, and this spasmodic or paroxysmal stage persists for weeks. How this paroxysmal stage originates, and why it should be so prolonged, has always intrigued investigators, and various hypotheses have been put forward. Among them is one suggested by Brown,<sup>3</sup> that a neurotropic toxin elaborated by the bacillus in the early catarrhal stage affects the vagus and respiratory centres and possibly the sensory nerve-endings in the upper respiratory mucosa. Fixation of this toxin in nervous tissue would explain the comparative failure of vaccines or convalescent serum to influence the course of the disease unless given in the incubation period or early in the catarrhal stage. Both exo- and endotoxins have been obtained from the Bordet-Gengou bacillus.

Ascorbic acid has been investigated by

several workers from the standpoint of its detoxicating action. Grootton and Bezsonoff<sup>4</sup> record the results of mixing diphtheria toxin and ascorbic acid, incubating very briefly, and injecting the mixture into guinea-pigs. Unneutralized ascorbic acid completely destroyed the toxic action, but this effect was one of pH and not a specific effect. Ascorbic acid neutralized with soda and mixed with the toxin so altered its potency that, of four guinea-pigs receiving 4 M.L.D. of toxin each, one survived and the others died respectively on the 4th, 6th, and 9th day. Controls injected with 4 M.L.D. each of unaltered toxin all died on the 2nd day. These workers, in the same paper, tested the actual bactericidal action of ascorbic acid against various bacteria by adding varying amounts of the acid to the culture medium, bringing the mixture to a pH of 7.0, and inoculating with such organisms as staphylococcus, streptococcus, gonococcus, typhosus, Bordet-Gengou, etc. With 0.5 per cent ascorbic acid mixtures only the gonococcus and Bordet-Gengou bacillus were inhibited, as compared with controls. The gonococcus grew readily in a 0.2 per cent mixture. In a percentage of 0.008, ascorbic acid inhibited the growth of the Bordet-Gengou bacillus. Glacial acetic acid added to the culture medium in corresponding amounts, and then neutralized, failed to affect the growth of this bacillus.

Woringer and Sala<sup>5</sup> reported 4 cases of whooping cough complicated by scurvy occurring among a series of infants treated in their clinic. No scurvy appeared among the other children, although all were on exactly the same dietary regimen. They suggest that vitamin C is an essential part of the body's defence against the Bordet-Gengou bacillus, and that excessive demands made in the presence of such an infection may so deplete the vitamin stores of the tissues as to lead to the clinical condition of scurvy.

Gander and Niederberger<sup>6</sup> and Hochwald<sup>7</sup> report the use of ascorbic acid in the treatment of pneumonias. Pneumonia cases showed con-

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sistently a deficit in vitamin C. Administration of the vitamin produced an effect comparable with that of specific serum. The pulse and temperature subsided by crisis when the avitaminosis was completely relieved, as shown by beginning urinary excretion of the ascorbic acid. When small doses of ascorbic acid were given, the saturation point for the vitamin was reached slowly, and no clinical improvement was shown until this point was reached.

Various investigators<sup>8, 9, 10</sup> have shown that the tissues of normal children and young animals contain more vitamin C than those of normal older subjects, and that the saturation point, as judged by beginning urinary excretion, is attained in young subjects only by much larger doses than relative weights would indicate. This suggests a greater need of vitamin C by young animals, and so a greater storage of it in the presence of an ample supply.

From this evidence, ascorbic acid seemed to have possibilities in the treatment of whooping cough, and one of us (B.M.U.) has been using

it in practice for the last two months or so. To date, we can report 9 cases, and 1 from another practitioner.\* In each case, diagnosis was made from a history of contact with known cases together with personal observation of the typical cough, vomiting and nocturnal paroxysms. Cough plates or serological tests were not used in this preliminary investigation. Condensed case reports follow.

#### DISCUSSION

The short series of cases presented is too small to draw any statistical conclusions, but one fact stands out. Ascorbic acid has a definite effect in shortening the period of paroxysms from a matter of weeks to a matter of days. We have not checked by cough plates or otherwise in this preliminary work to see whether the infectivity subsides simultaneously with the spasmodic symptoms, but are continuing with a larger series of cases in which these and other tests will be employed.

\* Case 4. We are indebted to Dr. C. H. A. Walton for details of this case.

TABLE

Case	Age (years)	Sex	Contact	Duration of Symptoms	Treatment	Results
1 R.T.	6	M	School	6 weeks—typical	150 mg. per day	7 days—cough reduced markedly 10 days—cough disappeared
2 C.H.	1½	M	Unknown Temperature 102 F. Bronchopneumonia when seen	3 weeks—typical 10 days “fever” at home	inhalations sinapisms } 3 days expectorants } 175 mg. daily—11 dys.	No effect 7 days—temperature normal, cough reduced 14 days—cough disappeared
3 M.C.	12	M	School	10 days—typical	200 mg. daily	6 days—cough reduced 13 days—only occasional night coughs 15 days—all cough absent
4 J.P.	6	F	School	over 4 weeks— typical	200 mg. daily	3 days—cough less, no vomiting 7 days—occasional cough
5 B.O.	2½	M	Known case	2 weeks—typical	250 mg. daily	5 days—cough disappeared
6 H.F.	7	M	School	2 weeks—typical	375 mg. daily	4 days—cough less 9 days—night cough only 11 days—all cough absent
7 E.H.	22		Maid Child in house had whooping cough	4 dys., paroxysmal cough, vomited once, no whooping	500 mg. daily—3 days 125 mg. daily	4 days—cough less, no vomiting 6 days—coughed only once in 2 days 11 days—cough absent
8 B.P.	4	M	Known case	10 days—typical	500 mg. daily—4 days 250 mg. daily—4 days	5 days—cough disappeared
9 M.W.	6½	F	School	2 weeks—typical	500 mg. daily—4 days 250 mg. daily—5 days	4 days—cough reduced 7 days—coughed once in 24 hours 9 days—cough disappeared
10 W. C.	4½	F	Sister (Case 9)	1 week—typical	500 mg. daily—4 days 250 mg. daily—5 days	Same as for Case 9

The dosages used have been empirical, with a tendency to use larger doses early in the disease as our experience of its effects progressed. The acid is available at reasonable prices, and the danger of overdosage seems negligible. Animals have received 2,000 times their estimated requirements without any deleterious effects. Any excess is excreted by the kidneys.

#### CONCLUSIONS

1. A method has been described for the treatment of whooping cough by ascorbic acid (vitamin C).

2. Ascorbic acid definitely shortens the paroxysmal stage of the disease, particularly if relatively large doses are used early in the disease.

The ascorbic acid used by us was the Hoffmann-LaRoche product sold under the trade name of "Red-

oxon". Grootton and Bezsonoff<sup>4</sup> have shown that this product is identical chemically, physically and biologically with the original product prepared by Szent-Gyorgi.

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## CHANGES IN CONDITIONED RESPONSES BROUGHT ABOUT BY ANÆSTHETICS AND SEDATIVES\*

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PAVLOV<sup>7</sup> (1927) and his co-workers first observed that conditioned salivary reflexes could be modified by drugs like alcohol, caffeine, chloral hydrate and bromide. Recently Wolff and Gantt<sup>8</sup> (1935) studied the effects of amytal upon conditioned salivary secretion. The object of the present research was to extend the work to conditioned alimentary-motor responses of dogs and cats. From this viewpoint we have re-investigated the influence of alcohol and of amytal, and tested several new drugs, namely nembutal, avertin, paraldehyde, bulbocapnine, carbon dioxide, ethylene, nitrous oxide, morphia, and hyoscine.

Two dogs and two cats served as subjects. The dogs received sodium amytal and nembutal intravenously, avertin per rectum, alcohol and paraldehyde by stomach tube, and morphia, hyoscine and bulbocapnine subcutaneously. The gaseous anæsthetics were administered to the cats under a bell jar. We naturally waited for full recovery from one drug before we administered a new drug or even a different dose of the same drug.

The general procedure for establishing conditioned reflexes is by now well known. The measured and recorded response may be salivary secretion or any other easily observed reaction (*cf.* Liddell, 1934).

In our work a lid-lifting response was used. This particular training procedure was described by Dworkin<sup>2</sup> (1935). The stimuli selected comprised auditory, visual and tactile signals. The successive tests were made at intervals of 2 to 6 minutes. During these intervals the animals had been trained not to touch the lid of the food container. Consistent absence of response between stimuli, eventually developed by training, may be called "interval inhibition" (Fig. 1A). The animals were also trained to make two discriminations, (1) between two different buzzers—"coarse" discrimination, (2) between a loud and a quiet musical tone of fixed frequency—"fine" discrimination. The time of incidence of the signals, as well as that of the animals' response, was recorded graphically. Thus we had information as to the latent period, presence or absence of conditioned response, duration of conditioned and unconditioned phases, and finally the amount of interval inhibition.

The latent period of the positive responses varied between 1 and 3 seconds. Often it was just as short for a visual as for a tactile or auditory stimulus. Nevertheless, a loud sound usually evoked a response sooner than a quiet sound; similarly, the latent period for a strong light was often shorter than for a weak light. When a negative stimulus was turned on for differentiation there was at times a slight turning of the head away from the food container, and other signs of general irritation, but no attempt to raise the lid (see Fig. 1B).

#### RESULTS

Our observations indicate that the eleven drugs tested may be classed into three main

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